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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,511	10/31/2003	George Nelson Bennett	61683-00002USPT	3571

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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/699,511	BENNETT ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *05/22/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Claims 1-7 are currently pending and under examination. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watson et al. (Biotechniques, 1997) and Liu et al. (Current Biology, 1998) in view of Stahl et al. (Biotechniques, 1993).

With regard to claim 1, Watson et al. teach a method of assembling PCR fragments comprising (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment):

a) making a first PCR fragment with first and second primers, wherein the second primer comprises a modified nucleotide that can be removed by a DNA repair enzyme, resulting in a 3' overhang (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment);

b) treating the first PCR fragment with a DNA repair enzyme to generate a 3' overhang

c) making a second PCR fragment with third and fourth primers, wherein the third and fourth primers each comprises a modified nucleotide that can be removed by a DNA repair enzyme resulting in a 3' overhang (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment);

d) treating the second PCR fragment with a DNA repair enzyme to generate a 3' overhang (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment);

e) annealing and ligating the first and second PCR fragments (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment);

f) optionally repeating steps c, d and e until a last PCR fragment is added to the growing chain to produce an assembled fragment (see p. 858 the abstract and p. 860 col. 3 under cloning of lac operon fragment),

g) circularizing the assembled fragment (see p. 860 col. 3 under cloning of lac operon fragment, where the fragment is circularized in the vector before transformation)

With regard to claim 2, Watson et al. teach one of the PCR fragments comprises an origin of replication and a selectable marker (see p. 860 col. 3 under cloning of lac operon fragment, the lac operon contains a selectable marker and the vector contains an origion of replication).

With regard to claim 3, Watson et al. teach the first PCR fragment or the last PCR fragment comprises an origin of replication and a selectable marker (see p. 860 col. 3 under cloning of lac operon fragment, the lac operon contains a selectable marker and the vector contains an origion of replication).

With regard to claim 5, Watson et al. teach the nucleotide is deoxyuridine and the DNA repair enzyme is Uracil-DNA-glycosylase followed by T4 endonuclease V (see p. 858 first full paragraph under introduction).

With regard to claims 6 and 7 Watson et al. teach the assembled DNA is greater than 30 kb see p. 860 col. 3 under cloning of lac operon fragment where the lac operon and the vector are greater than 30 kb).

With regard to step (a) Watson et al. do not teach using site specific recombination.

With regard to step (g) Watson et al. do not teach circularization with a site specific recombinase.

With regard to steps (a) and (g) Liu et al. teach site specific recombination and circularization with recombinase (see p. 1301 under results).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of using the cre/lox recombinase system as taught by Liu with the method of DNA assembly as taught by Watson in order to reduce the time and effort associated with restriction mediated DNA assembly. Liu et al. state, "UPS eliminates the use of restriction enzymes and DNA ligase: instead, these functions are both carried out simultaneously by a single enzyme Cre. This relieves the constraints on cloining vectors with respect to DNA sequence and size because the UPS reaction is independent of vector size or sequence. Furthermore, the time-consuming processes inherent in conventional cloning such as the identification of a suitable vector, designing a cloning strategy, restriction endonuclease digestion, agarose gel electrophoresis, isolation of DNA fragments, and the ligation reaction is shortened to a 20 minute UPS reaction (see p. 1307 col. 1 lines 8-19 under Discussion)." It would have been prima facie obvious to apply the cre/lox recombinase system as taught by Liu with the method of DNA assembly as taught by Watson in order to have increased efficiency in assembling DNA fragments. The use of cre/lox recombinase system provides for rapid and efficient generation and manipulation of recombinant DNA.

With respect to step (b) Watson et al. and Liu et al. do not teach immobilizing the PCR fragments for assembly.

With regard to step (g) Watson et al. and Liu et al. do not teach removing the assembled fragment from the solid support.

Stahl et al. teach immobilizing PCR fragments for assembly (see p. 424 abstract and p. 425 Figure 1).

Stahl et al. teach subsequently removing the assembled gene construct from the bead prior to subcloning (see p. 426 col. 2 first full paragraph).

One of ordinary skill in the art at the time the invention was made would have been motivated to apply the step of immobilizing the fragments for assembly as taught by Stahl with the method of DNA assembly as taught by Watson and Liu in order to have a controlled assembly of the fragments. Stahl et al. state, "Immobilization of the first oligonucleotide enables controlled stepwise annealing/ligation of successive 5' phosphorylated oligonucletides to rapidly build up accurate gene constructs making it possible to sub clone for subsequent expression of the gene product (see p. 424 col. 3 first full paragraph)." It would have been prima facie obvious to apply the step of immobilizing the fragments for assembly as taught by Stahl with the method of DNA assembly as taught by Watson and Liu in order to stabilize and control the assembly of the gene constructs. Controlled assembly yields more accurate gene constructs.

Response to Arguments

4. Applicants' arguments with respect to the rejections over Watson et al. and Liu et al. in view of Stahl et al. have been fully considered but are not persuasive. Applicants argue the references do not tech the added benefit of circularizing and releasing the assembled DNA in a single event by recombination. This is not persuasive because the references are not required to teach Applicants' motivation. Here the benefit of removing and circularizing are clearly addressed by Liu and Stahl. Liu teaches the advantages of the fusion and circularization using a site specific recombination system when Liu teaches UPS eliminates the use of restriction enzymes and DNA ligase: instead, these functions are both carried out simultaneously by a single enzyme Cre. This relieves the constraints on cloining vectors with respect to DNA sequence and size because the UPS reaction is independent of vector size or sequence. Furthermore, the time-consuming processes inherent in conventional cloning such as the identification of a suitable vector, designing a cloning strategy, restriction endonuclease digestion, agarose gel electrophoresis, isolation of DNA fragments, and the ligation reaction is shortened to a 20 minute UPS reaction (see p. 1307 col. 1 lines 8-19 under Discussion). Additionally, Stahl teaches the advantages of

immobilizing PCR fragments for gene synthesis on a solid support. Stahl teaches that immobilization of the first oligonucleotide enables controlled stepwise annealing/ligation of successive 5' phosphorylated oligonucletides to rapidly build up accurate gene constructs making it possible to sub clone for subsequent expression of the gene product (see p. 424 col. 3 first full paragraph). Both Liu and Stahl clearly teach a motivation for why it would be advantageous to use their methods with the method of Watson. The motivation found in Liu and Stahl is not the same motivation disclosed by Applicants' but this is permissible as the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

With respect to Applicants' arguments regarding impermissible hindsight, Applicants argue again there is no motivation to combine the references. Applicants argue the references are not related and should not be combined. This argument is not persuasive because Watson et al. is concerned with assembling PCR products and cloning into a vector. Liu teach cloning methods that facilitate the systematic construction of recombinant DNA molecules (i.e. assembling PCR products into a vector). Finally Stahl teaches the synthesis of a gene on a solid support and the advantages of immobilizing the fragments on a solid support for assembly. These references are in the field of Applicants' endeavor and are pertinent to improving gene assembly.

Applicants' repeatedly, argue that the references do not teach single step removal and circularization. This is not persuasive because Applicants are arguing a limitation which is not present in the claims. Nowhere do the claims require that the removal and circularization occur in a single step.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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hgc

TERESA E. STRZELECKA, PH.D.
PRIMARY EXAMINER

Teresa Strzelecka
7/20/06